REMARKS

Claims 13, 17, and 19-42 are pending in the application. Claims 13, 17, and 19-38 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 39-42 are currently being examined on the merits. Claim 39 has been amended to further clarify the intended subject matter of the claimed invention. Support for the amendments is found in the specification at, for example, page 2, lines 21-24, page 38, lines 10-12, and page 18, lines 24-26. No new matter is added by these amendments. Entry of these amendments is respectfully requested.

Rejections under 35 U.S.C. §§ 101/112, first paragraph:

Claims 39-42 are rejected under 35 U.S.C. § 101, as allegedly lacking either a substantial, specific asserted utility or a well established utility. In particular, the Examiner asserts that "neither the specification nor any art of record demonstrates a correlation between the overexpression of SCAH-2 or lack thereof and the presence of a pathophysiological disease state" (Office Action, page 2). The Examiner also asserts that "the function of the SEQ ID NO:2 polypeptide could not be anticipated" (Office Action, page 4) based upon the evidence provided in the specification.

The claimed SCAH-2 polypeptide, having the amino acid sequence of SEQ ID NO:2, was identified as a stem cell antigen in part due to chemical and structural homology with other known stem cell antigens. While acknowledging that SCAH-2 shares 27% amino acid sequence identity with chicken stem cell antigen-2, the Examiner attaches great significance to the fact that the sequences also show a 73% dissimilarity. The Examiner argues that Bowie et al. teach that certain positions of a protein sequence are critical to the three-dimensional structure and function of the protein and therefore can tolerate only conservative substitutions or no substitutions (Office Action, page 3). Applicants respectfully direct the Examiner's attention to Bowie et al. at page 1306, column 2, wherein the authors state that "proteins are surprisingly tolerant of amino acid substitutions," and that "at some positions, many different nonconservative substitutions were allowed." It is well-known in the art that natural selection tends to conserve those residues critical for protein structure and function during the course of evolution. This is why the study of a set of related sequences can indicate which residues are critical, since these are the ones which are conserved between sequences of different species (See Bowie et al., page 1306, and pages

1308-1309).

For example, in the case of the Ly-6 family proteins it is well known in the art that the members of this family contain 10 conserved cysteine residues (R.G.E. Palfree "Ly-6-domain proteins - new insights and new members: a C-terminal Ly-6 domain in sperm acrosomal protein SP-10" Tissue Antigens (1996) 48:71-79). As shown in Figure 3, SCAH-2 conserves all 10 of these characteristic cysteine residues (see also the specification, page 6, lines 15-19). While the number and spacing of the 10 cysteine residues is characteristic of the family, "they provide a framework for considerable sequence diversity among the relatives" (Palfree, page 72, col. 1). Thus the Examiner has provided no reason why one of skill in the art would not believe that the 27% amino acid identity between SCAH-2 and chicken stem cell antigen-2, (a level of identity similar to that between other family members, as shown in Figure 1 of Palfree), together with the presence of the conserved cysteine residues, would in fact be sufficient to conserve the structural and functional properties between the two proteins.

The other examples cited by the Examiner, Burgess et al. and Lazar et al., fail to provide support for the Examiner's position, since both discuss the effects of artificial, site-directed mutations of residues selected in the belief that they were essential for protein function. Indeed, the sites for mutation in Lazar et al. were specifically chosen based upon the fact that "these two amino acids are highly conserved in the EGF-like family of peptides." (Lazar et al., page 1247, col. 1). It is hardly surprising that these amino acid substitutions had significant effects on protein function, but such mutations are precisely those that would be selected against during the course of evolution. Applicants note, for instance, that while the family of EGF-like peptides shares only about 35% amino acid homology (Lazar et al., page 1247, col. 1) the two amino acids found by Lazar et al. to be important for protein function were highly conserved across the entire family. The examples cited by the Examiner are therefore irrelevant to the question of whether a naturally-occurring sequence retains the function of its homolog, as is the case here.

The Examiner also relies upon the paper by Bork, to argue that sequence analysis of SCAH-2 cannot be used to reliably predict the protein's function. Applicants respectfully suggest that the Examiner attempts to draw too sweeping conclusions from Bork. It may be true that the use of sequence analysis to predict protein function is not 100% percent accurate (although still, based upon Bork's figure of 70% accuracy, more likely than not to be correct) as the quality of data in the public sequence databases is still insufficient to perfectly annotate every

new sequence. However, this is a general conclusion; one of skill in the art would clearly understand that the likelihood of a prediction being correct for a particular sequence depends upon how much data is available for the particular family to which it belongs. As discussed in Bowie et al. "[t]here is more information in a set of related sequences than in a single sequence" (page 1309, col. 2).

Applicants also respectfully direct the Examiner's attention to the enclosed BLAST results of SCAH-2 against the Genpept database (Exhibit A) which shows that all of the ten hits which have known functions are stem cell antigens. Thus, there is no reason for one of ordinary skill in the art to believe that SCAH-2 is not in fact a stem cell antigen.

The Examiner further asserts that "the specification provides no objective evidence to indicate that the polynucleotide of SEQ ID NO:4 is actually translated in vivo into the polypeptide of SEQ ID NO:2 and that the level of said SEQ ID NO:2 is actually correlated with a disease state" (Office Action, page 5). In support of these assertions the Examiner cites references teaching that in certain cases protein expression is regulated at the translational level. These examples refer to situations in which, for example, the translation of ferritin or the transferrin receptor is regulated by levels of iron. No evidence is provided that such a mechanism is involved in regulating the expression of any known stem cell antigen. Nor do these cases refute the obvious presumption that SEQ ID NO:2 is translated into SCAH-2 in at least some situations.

In addition, Applicants respectfully point out that, as disclosed in the specification, the sequence encoding SCAH-2 was first isolated from a bladder tumor cDNA library (specification, page 6, lines 29-33), the preparation of which is described in the specification in Example I (page 32). This evidence indicates an association of SCAH-2 expression with cancer. Give w DNA ?

Applicants also respectfully direct the Examiner's attention to the enclosed paper (Reiter, R.E. et al. "Prostate stem cell antigen: A cell surface marker overexpressed in prostate cancer" Proc. Natl. Acad. Sci. USA (1998) 95:1735-1740). This post-filing reference discloses a protein having an amino acid sequence with 99% identity to SEQ ID NO:2 (differing only at the position of the "X" residue in SEQ ID NO:2), referred to as prostate stem cell antigen (PSCA). Like the other members of the Ly-6 family, PSCA is a GPI-anchored glycoprotein expressed on the cell surface (Reiter, page 1738). PSCA is predominantly prostate-specific in normal tissues and is overexpressed in over 80% of prostate cancers (Reiter, page 1739, column 1).

The data disclosed in this reference serve to confirm Applicants' assertion that SCAH-2 is a stem cell antigen, based upon the disclosed homology to chicken stem cell antigen-2 , the presence of conserved cysteine residues, and the identification of cDNAs encoding SCAH-2 in tumor tissues. This data also confirms that SEQ ID NO:4 is in fact translated into the polypeptide of SEQ ID NO:2, and that this polypeptide is involved in a human disease. Thus the one of skill in the art would readily understand that the claimed polypeptides would be useful in, for example, the screening and diagnosis of cancer, without any further experimentation.

Applicants note that the association of SCAH-2 with tumors and the use of SCAH-2 in screening, diagnosis and treatment of cancers was asserted in the specification at, for example, page 3, lines 9-14, and page 18, lines 12-17 wherein the specification states that "[s]ince a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and a more malignant phenotype, the SCAH-1 and SCAH-2 proteins can be used to identify antibodies, antagonists, and inhibitors which would diminish the efficiency of local tumor growth without inducing cell proliferation." Methods for diagnostic assays and drug screening are disclosed in the specification at, for example, pages 20-21.

Any of the uses described above in screening, diagnosis, drug development, and treatment of cancers already meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need

> only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The burden on the Office to demonstrate lack of utility is high. Case law has set forth the following standards in the determination of lack of utility:

> Some degree of utility is sufficient for patentability; further, defense of non-utility cannot be sustained without proof of **total incapacity**. *Envirotech Corporation v. Al George, Inc.*, 221 USPQ 473 (Fed. Cir. 1984). (Emphasis added.)

As further clarified *In In re Cortright* 49 USPQ2d 1466 (Fed. Cir. 1999):

> ...an applicant's failure to disclose how to use an invention may support a rejection under...section 101 for lack of utility 'when there is a **complete absence** of data supporting the statements which set forth the desired results of the claimed invention.' (Emphasis added.) *Envirotech Corporation v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984).

Clearly, the Examiner has not demonstrated total incapacity of Applicants's claimed invention, nor is there a "complete absence" of data supporting the statements of utility in

Applicants' specification. The rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved.

Claims 39-42 were also rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the instant invention (Office Action, page 6). The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Based on the above evidence and reasoning, Applicants submit that the rejection of claims 39-42 under 35 U.S.C. §§ 101/112, first paragraph is improper. Withdrawal of this rejection is respectfully requested.

Enablement rejections under 35 U.S.C.§ 112, first paragraph:

The Examiner asserts that "the specification does not reasonably provide enablement for immunogenic or biologically active fragments of SEQ ID NO:2, or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2" (Office Action, page 6).

With respect to variants of SEQ ID NO:2, the Examiner asserts that "Given the lack of guidance in the specification for choosing which amino acid residues of SEQ ID NO:2 will tolerate substitution, either separately or in groups, and which specific amino acids can be substituted in at any specified location, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the claimed invention" (Office Action, pages 7-8).

Applicants respectfully point out that the claims are directed to naturally-occurring variants of SEQ ID NO:2. Thus it is not necessary to screen all conceivable variants which might be made using recombinant methods, as all that is claimed are those variants which are found in nature. Given the sequence of SEQ ID NO:2 one of ordinary skill in the art could readily identify a naturally occurring polypeptide having at least 90% identity to SEQ ID NO:2 using well known methods of sequence analysis, without any undue experimentation. The skilled artisan would also know how to use the claimed polypeptides, for example in screening and diagnosis of cancer as discussed above.

Applicants also note that in order to clarify the intended subject matter of the claimed

invention, claim 39(b) has been amended to require that the claimed variants are expressed on the surface of stem cells. Support for this amendment is found in the specification at, for example, page 2, lines 21-24, wherein the specification discloses that the claimed SCAH-2 polypeptide has "characteristics of the LY-6 family of cysteine rich proteins which are expressed on the surface of lymphoid cells." Assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, page 38, lines 10-12. Thus the skilled artisan would have additional guidance in making and using the claimed variants.

With respect to the claimed biologically active fragments, the Examiner asserts that "one of skill in the art could not anticipate what amino acid sequence(s) would retain the function of the SCAH-2 polypeptide" and cites references pertaining to the three-dimensional structures of proteins (Office Action, page 8). Applicants note that in order to clarify the intended subject matter of the claimed invention, claim 39(c) has been amended to recite "a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment is expressed on the surface of stem cells". Assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, page 38, lines 10-12. It is not necessary for the specification to list the sequences of all the biological fragments encompassed by the claims, since one of ordinary skill in the art would be able to identify and use those biologically active fragments retaining the required activity by following the guidance in the specification, without any undue experimentation.

With respect to the claimed immunologically active fragments, the Examiner asserts that the specification does not teach any examples of immunologically active fragments. The Examiner further asserts that "[t]he determination of an immnogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 polypeptide which have been determined to be immunogenic fragments in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed."

Applicants respectfully point out that the generation of antibodies to proteins is well known in the art and is routinely successful without knowledge of the crystal structure of the protein, in contrast to the assertions of the Examiner (Office Action, pages 9-10). In addition, the specification provides further guidance as to the selection of immunogenic fragments. See, for example, page 38, lines 15-21, wherein the specification describes software programs used to

determine regions of high immunogenicity and also discloses that appropriate epitopes may include "those near the C-terminus or in hydrophilic regions". A hydrophobicity plot for SCAH-2 is provided in Figure 5. Based upon all of this guidance, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:2 without any undue experimentation.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102:

The rejection of claim 39 under 35 U.S.C. § 102 as allegedly being anticipated by the six listed references was maintained. The Examiner asserts that these references disclose immunogenic polypeptide fragments of SEQ ID NO:2. The Examiner does not appear to have provided any sequence alignment that would show the location of these putative immunogenic fragments. Applicants also note that none of the proteins in the listed references is found in a BLAST search of the Genbank protein sequence database (see Exhibit A), indicating that the reference proteins (none of which appears to be in the family of stem cell antigens) must have extremely low overall homology to SEQ ID NO:2. Applicants have performed sequence alignments using the CLUSTALW algorithm between the polypeptide of SEQ ID NO:2 and those of Burton et al. and Wray and Fisher (see Exhibit B). In the other cases it was not possible to determine which of several polypeptides was referred to. As shown in Exhibit B, both reference polypeptides have at best only two consecutive amino acid residues in common with SEQ ID NO:2.

Claim 39(d) has been amended to recite "an immunogenic fragment of the amino acid sequence of SEQ ID NO:2, wherein said immunogenic fragment comprises at least 5 contiguous amino acids of SEQ ID NO:2 and is capable of generating an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:2." Support for this claim limitation is found in the specification at page 18, lines 24-26, wherein the specification discloses that "[p]eptides used to induce specific antibodies may have an amino acid sequence consisting of at least 5 amino acids". None of the reference polypeptides shares more than two amino acids in common with SEQ ID NO:2; thus these reference polypeptides do not anticipate the claims. Withdrawal of the rejection of claim 39 under 35 U.S.C. § 102 is therefore respectfully requested.

Missing IDS references

Applicants understand that the Examiner was not able to locate the IDS references lined through in the previous office action. As stated in Applicants' previous response, these references were already submitted in the parent file. As a gesture of cooperation, Applicants hereby submit copies of these missing references. Applicants sincerely wish that the Patent and Trademark Office safeguard the references in this and the parent file, and thus both the Examiner and Applicants would save their time in locating additional copies.

Withdrawal of all other rejections and objections

Applicants would like to thank the Examiner for withdrawing all other rejections and objections as recited in the previous office action, paper number 7.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 39 has been amended as follows:

39. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:2,

b) an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, wherein said amino acid sequence [is a member of the sca-2 family polypeptides] is expressed on the surface of stem cells,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment [is a member of the sca-2 family polypeptides] is expressed on the surface of stem cells, and

d) an immunogenic fragment of the amino acid sequence of SEQ ID NO:2, wherein said immunogenic fragment comprises at least 5 contiguous amino acids of SEQ ID NO:2 and is capable of generating an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:2.